REMARKS

Claims 1-92 are pending. Claims 48-51, 54, 57, 59-61, 66-69, 72, 75, 78-80, 91 and 92 are under examination. New claims 93-96 have been added. Claims 48, 49, 66, and 67 have been amended. Support for the amendments and new claims can be found throughout the specification and the claims as filed. In particular, support for amendments to claims 48 and 66 can be found in paragraphs [037] and [064] in the application as filed. Support for amendments to claims 49 and 67 can be found in paragraph [045]. Support for new claims 93-96 can be found in paragraphs [0060], and [0130]-[0133].

Accordingly, these amendments and new claims do not raise an issue of new matter and entry thereof is respectfully requested.

Applicants wish to the thank the Examiner for granting a telephonic interview conducted February 3, 2010.

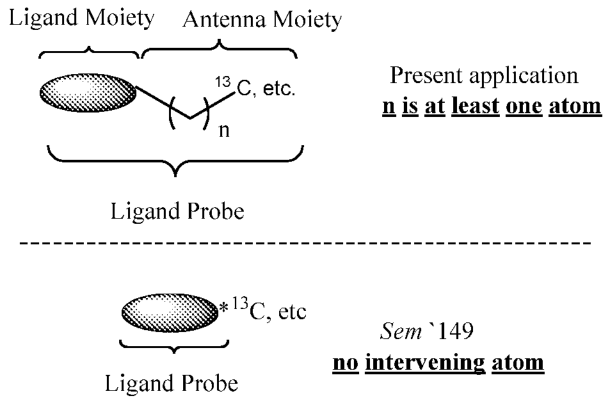
Claim Objection

The Examiner has objected to claims 60 and 61 for having erroneous claim status identifiers. Applicants have corrected the status identifiers and respectfully request removal of this objection.

Claim rejections under 35 U.S.C. §102

The rejection of claims 48-51, 54, 57, 59-61, 66-69, 72, 75, 78-80, 91, and 92 under 35 U.S.C. §102 as allegedly being anticipated by Sem, U.S. 6,333,149 ("*Sem*") is respectfully traversed.

Although Applicants assert that the claims were patentable over *Sem* as previously presented, in the interest of moving prosecution forward Applicants have amended independent claims 48 and 66 to recite all portions of the ligand probe and distinguish the ligand probe of claims 48 and 66 from the ligand probe of *Sem* as indicated in the figure below:



As indicated in the figure, *Sem* does not show the claim element of the antenna moiety. Instead, the *Sem* system is a ligand probe that is a labeled common ligand lacking at least one atom intervening between a ligand moiety (or common ligand) and the NMR visible nucleus of an antenna moiety. The atom(s) of the antenna moiety provide(s) additional features not present in the *Sem* system including: 1) extending the range over which a second ligand can be detected; 2) providing flexibility in the antenna moiety to provide access to additional conformers to extrapolate additional information and/or enhance information related to, for example, the relative orientation between atom groups on the ligand moiety (or common ligand) and/or the second ligand; and 3) the antenna moiety can be readily altered as part of combinatorial optimization to map candidate linkers for the preparation of bi-ligands (i.e. common ligand covalently linked to a second ligand).

With regard to the first point, in the specification at paragraph [060], (see also new claims 94 and 96) it is noted that an NOE is observed for atoms that are about 6 angstroms apart or closer. However, a ligand moiety (or common ligand) and a second ligand that are further apart than about 6 angstroms when bound to a protein, would not have an observable NOE when employing the *Sem* method. Accordingly, the presence of an antenna moiety to extend the reach of the ligand moiety of the ligand probe towards a second ligand permits the discovery of second ligands that would otherwise have been missed because they are further than 6 angstroms from the ligand probe employed by *Sem*. Thus, ligand probes of the present invention, unlike the ligand probe of *Sem*, can be used to discover second ligands that are 7 angstroms, 8 angstroms, 9 angstroms, or 10 angstroms away, or more. Since each C-C bond has a length of 1.54 angstroms, and C-O, C-F, C-P bonds are in the range of 1-3 angstroms, (see the exemplary bond lengths

tabulated in Exhibit A), adding 1, 2, or 3 additional atoms in the form of an antenna moiety can extend the reach of the ligand probe an additional 1.5-5 angstroms, for example. Further atom insertions providing an even longer antenna moiety would extend the reach of the ligand probe even further, thereby permitting discovery of ligands, using NOE measurements, that would not have been discovered using a ligand probe lacking an antenna moiety.

Anticipation requires recitation of all the claim elements in substantially the same manner as claimed. Because *Sem* does not disclose an antenna moiety. Independent claims 48 and 66, and claims dependent therefrom, are patentable over *Sem*. Applicants respectfully request withdrawal of this rejection.

Double Patenting

For at least the reasons presented above, Applicants assert that claims 48-51, 54, 57, 59-61, 66-69, 72, 75, 78-80, 91 and 92 are not subject to non-statutory obviousness-type double patenting over claim 1-33 of *Sem* (as cited above), claims 1-62 of U.S. patent 6,620,589, claims 1-160 of U.S. patent 6,797,460, and claims 1-42 of U.S. patent 7,252,931.

Conclusion

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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BOND LENGTHS BETWEEN CARBON AND OTHER ELEMENTS

Prepared by Olga Kennard.

The tables are based on bond distance determinations, by experimental methods, mainly X-ray and electron diffraction, and include values published up to January 1, 1956. In the present tables, for the sake of completeness individual values of bond distances of lower accuracy are quoted with limits of error indicated where possible. Values for tungsten and bismuth should be treated with particular caution.

According to the statistical theory of errors if an average quantity $\bar{\mu}$ and a standard deviation σ can be evaluated there is a 95% probability that the true value lies within the interval $\bar{\mu} \pm 2\sigma$. Too much reliance should, however, not be placed on σ values in bond distance determinations since the derivation of these certain sources of error may have been neglected.

Values of the bond lengths and the limits of error are each given in Ångstrom units.

BOND LENGTHS BETWEEN CARBON AND OTHER ELEMENTS

Reference: HCP and "Tables of interatomic distances" Chem. Soc. of London, 1958

Group	Bond type	Element						
I	All types	H**						
		1.056 – 1.115						
II		Be	Hg					
		1.93	2.07 ± 0.01					
III		B	Al	In				
		1.56 ± 0.01	2.24 ± 0.04	2.16 ± 0.04				
IV	All types	C**	Ge	Si	Sn	Pb		
	Alkyls (CH_3XH_3)	1.54 – 1.20	1.98 ± 0.03	1.865 ± 0.008	2.143 ± 0.008	2.29 ± 0.05		
	Aryl ($C_6H_5XH_3$)			1.84 ± 0.01	2.18 ± 0.02			
	Neg. Subst. (CH_3XCl_3)			1.88 ± 0.01				
V	All types	N**	P	As	Sb	Bi		
	Paraffinic $(CH_3)_3X$	1.47 – 1.1	1.87 ± 0.02	1.98 ± 0.02	2.202 ± 0.016	2.30*		
VI		O**	S**	Cr	Se	Te	Mo	W
		1.43 – 1.15	1.81 – 1.55	1.92 ± 0.04	1.98 – 1.71	2.05 ± 0.14	2.08 ± 0.04	2.06 ± 0.01*
VII	Paraffinic (monosubstituted)	F	Cl	Br	I			
	(CH_3X)	1.831 ± 0.005	1.767 ± 0.002	1.937 ± 0.003	2.13_5 ± 0.01			
	Paraffinic (disubstituted) (CH_2X_2)	1.334 ± 0.004	1.767 ± 0.002	1.937 ± 0.003	2.13_5 ± 0.1			
	Olefinic (CH_2:CHX)	1.32_5 ± 0.1	1.72 ± 0.01	1.89 ± 0.01	2.092 ± 0.005			
	Aromatic (C_6H_5X)	1.30 ± 0.01	1.70 ± 0.01	1.85 ± 0.01	2.05 ± 0.01			
	Acetylenic (HC:CX)		1.635 ± 0.004	1.79_5 ± 0.01	1.99 ± 0.02			
VIII		Fe	Co	Ni	Pd			
		1.84 ± 0.02	1.83 ± 0.02	1.82 ± 0.03	2.27 ± 0.04			

* Error uncertain.
** See following individual tables.

CARBON-CARBON

Single Bond	
Paraffinic	1.541 ± 0.003
In diamond (18°C)	1.54452 ± 0.00014
Partial Double Bond	
(1) Shortening of single bond in presence of carbon carbon double bond, e.g. $(CH_3)_2C{:}CH_2$; or of aromatic ring e.g. $C_6H_5 \cdot CH_3$	1.53 ± 0.01
(2) Shortening in presence of a carbon oxygen double bond e.g. CH_3CHO	1.516 ± 0.005
(3) Shortening in presence of two carbon-oxygen double bonds, e.g. $(CO_2H)_2$	1.49 ± 0.01
(4) Shortening in presence of one carbon-carbon triple bond, e.g. $CH_3 \cdot C\vdots CH$	1.460 ± 0.003
(5) In compounds with tendency to dipole formation, e.g. C:C.C$\vdots$N	1.44 ± 0.01
(6) In graphite (at 15°C)	1.4210 ± 0.0001
(7) In aromatic compounds	1.395 ± 0.003
(8) In presence of two carbon carbon triple bonds, e.g. HC$\vdots$C.C$\vdots$CH	1.373 ± 0.004
Double Bond	
(1) Simple	1.337 ± 0.006
(2) Partial triple bond, e.g. CH_2:C:CH_2	1.309 ± 0.005
Triple Bond	
(1) Simple, e.g. C_2H_2	1.204 ± 0.002
(2) Conjugated, e.g. $CH_3 \cdot (C{:}C)_2 \cdot H$	1.206 ± 0.004

CARBON-HYDROGEN

(1) Paraffinic (a) in methane	1.091
(b) in monosubstitured carbon	1.101 ± 0.003
(c) in disubstituted carbon	1.073 ± 0.004
(d) in trisubstituted carbon	1.070 ± 0.007
(2) Olefinic, e.g. CH_2:CH_2	1.07 ± 0.01
(3) Aromatic in C_6H_6	1.084 ± 0.006
(4) Acetylenic, e.g. CH$\vdots$C.X	1.056 ± 0.003
(5) Shortening in presence of a carbon triple bond, e.g. CH_3CN	1.115 ± 0.004
(6) In small rings, e.g. $(CH_2)_2S$	1.081 ± 0.007

CARBON-NITROGEN

Single Bond	
(1) Paraffinic (a) 4 co-valent nitrogen	1.479 ± 0.005
(b) 3 co-valent nitrogen	1.472 ± 0.005
(2) In C–N= e.g. CH_3NO_2	1.475 ± 0.010
(3) Aromatic in $C_6H_5NHCOCH_3$	1.426 ± 0.012
(4) Shortened (partial double bond) in heterocyclic systems, e.g. C_5H_5N	1.352 ± 0.005
(5) Shortened (partial double bond) in N–C=O e.g. $HCONH_2$	1.322 ± 0.003
Triple Bond	
(1) in R.C:N	1.158 ± 0.002

BOND LENGTHS BETWEEN CARBON AND OTHER ELEMENTS (Continued)

CARBON-OXYGEN

Single Bond

(1) Paraffinic	1.43 ± 0.01
(2) Strained e.g. epoxides	1.47 ± 0.01
(3) Shortened (partial double bond) as in carboxylic acids or through influence of aromatic ring, e.g. salicylic acid	1.36 ± 0.01

Double Bond

(1) In aldehydes, ketones, caboxylic acids, esters	1.23 ± 0.01
(2) In zwitterion forms, e.g. DL serine	1.26 ± 0.01
(3) Shortened (partial triple bond) as in conjugated systems	1.207 ± 0.006
(4) Partial triple bond as in acyl halides or isocyanates	1.17 ± 0.01

CARBON-SULPHUR

Single Bond

(1) Paraffinic, e.g. CH_3SH	1.81(5) ± 0.01
(2) Lengthened in presence of fluorine, e.g. $(CF_3)_2S$	1.83(5) ± 0.01
(3) Shortened (partial double bond) as in heterocyclic systems, e.g. C_4H_4S	1.73 ± 0.01

Double Bond

(1) In ethylene thiourea	1.71 ± 0.02
(2) Shortened (partial triple bond) in presence of second caron double bond, e.g. COS	1.558 ± 0.003

BOND LENGTHS OF ELEMENTS

Element	Bond	Å
Ac	Ac–Ac	3.756
Ag (25°C)	Ag–Ag	2.8894
Al (25°C)	Al–Al	2.863
As	As–As	2.49
As_4	As–As	2.44 ± 0.03
Au (25°C)	Au–Au	2.8841
B_2	B–B	1.589
Ba (room temp.)	Ba–Ba	4.347
Be (α-form, 20°C)	Be–Be	2.2260
Bi (25°C)	Bi–Bi	3.09
Br_2	Br–Br	2.290
Ca (α-form, 18°C)	Ca–Ca	3.947 (f.c.c.)
(β-form, 500°C		3.877 (b.c.c.)
Cd (21°C)	Cd–Cd	2.9788
Cl_2	Cl–Cl	1.988
Ce	Ce–Ce	3.650
Co (18°C)	Co–Co	2.5061
Cr (α-form, 20°C)	Cr–Cr	2.4980
(β-form, >1850°C		2.61
Cs (−10°C)	Cs–Cs	5.309
Cu (20°C)	Cu–Cu	2.5560
Dy	Dy–Dy	3.503
Er	Er–Er	3.468
Eu	Eu–Eu	3.989
F_2	F–F	1.417 ± 0.001
Fe (α-form, 20°C)	Fe–Fe	2.4823 (b.c.c.)
(γ-form, 916°C)		2.578 (f.c.c.)
(δ-form, 1394°C)		2.539 (b.c.c.)
Ga (20°C)	Ga–Ga	2.442
Gd (20°C)	Gd–Gd	3.573
Ge (20°C)	Ge–Ge	2.4498
H_2	H–H in H_2	0.74611
	H–D in HD	0.74136
	D–D in D_2	0.74164
He	He–He in $[He_2]^+$	1.08_6
Hf (α-form, 24°C)	Hf–Hf	3.1273 (h.c.p.)
Hg (−46°C)	Hg–Hg	3.005
Ho	Ho–Ho	3.486
I_2	I–I	2.662
In (20°C)	In–In	3.2511
Ir (room temp.)	Ir–Ir	2.714
K (78°K)	K–K	4.544
La (α-form)	La–La	3.739 (h.c.p.)
(β-form)		3.745 (f.c.c.)
Li (20°C)	Li–Li	3.0390
Lu	Lu–Lu	3.435
Mg (25°C)	Mg–Mg	3.1971
Mn (γ-form, 1095°C)	Mn–Mn	2.7311 (f.c.c.)
(δ-form, 1134°C)		2.6679 (b.c.c.)
Mo (20°C)	Mo–Mo	2.7251
N_2	N–N	1.0975_8 ± 0.0001
Na (20°C)	Na–Na	3.7157
Nb (20°C)	Nb–Nb	2.8584
Nd	Nd–Nd	3.628
Ni (18°C)	Ni–Ni	2.4916
Np (α-form, 20° C)	Np–Np	2.60 (orthorhombic)
(β-form, 313°C)		2.76 (tetragon)
(γ-form, 600°C)		3.05 (b.c.c.)
O_2	O–O	1.208
O_3 angle 116.8 ± 0.5°		1.278 ± 0.003
Os (20°C)	Os–Os	2.6754
P black	P–P	2.18
P_4	P–P	2.21 ± 0.02
Pa	Pa–Pa	3.212
Pb (25°C)	Pb–Pb	3.5003
Pd (25°C)	Pd–Pd	2.7511
Po (α-form, 10°C)	Po–Po	3.345 (cubic)
(β-form, 75°C)		3.359 (rh. hedr.)
Pr (α-form)	Pr–Pr	3.640 (tetrag.)
(β-form)		3.649 (f.c.c.)
Pt (20°C)	Pt–Pt	2.746
Pu (γ-form, 235°C)	Pu–Pu	3.026 (f.c.c.)
(δ-form, 313°C)		3.279 (f.c.c.)
(ε-form, 500°C)		3.150 (b.c.c.)
Rb (20°C)	Rb–Rb	4.95
Re (room temp.)	Re–Re	2.741
Rh (20°C)	Rh–Rh	2.6901
Ru (25°C)	Ru–Ru	2.6502
S_2	S–S	1.887
S_8	S–S	2.07 ± 0.02
Sb (25°C)	Sb–Sb	2.90
Sc (room temp.)	Sc–Sc	3.212
Se (20°C)	Se–Se	2.321
Se_2	Se–Se	2.152 ± 0.003
Se_8	Se–Se	2.32 ± 0.003
Si (20°C)	Si–Si	2.3517
Sn (α-form, 20°C)	Sn–Sn diamond	2.8099
(β-form, 25°C)	type lattice	3.022 (tetrag.)
Sr (α-form, 25°C)	Sr–Sr	4.302 (f.c.c.)
(β-form, 248°C)		4.32 (h.c.p.)
(γ-form, 614°C)		4.20 (b.c.c.)
Ta (20°C)	Ta–Ta	2.86
Tb	Tb–Tb	3.525
Tc (room temp.)	Tc–Tc	2.703
Te (25°C)	Te–Te	2.864
Th (α-form, 25°C)	Th–Th	3.595 (f.c.c.)
(β-form, 1450°C)		3.56 (b.c.c.)
Ti (α-form, 25°C)	Ti–Ti	2.8956 (h.c.p.)
(β-form, 900°C)		2.8636 (b.c.c.)
Tl (α-form, 18°C)	Tl–Tl	3.4076 (h.c.p.)
(β-form, 262°C)		3.362 (b.c.c.)
Tm	Tm–Tm	3.447
U (α-form)	U–U	2.77
(β-form, 805°C)		3.058 (b.c.c.)
V (30°C)	V–V	2.6224
W (25°C)	W–W	2.7409
Y	Y–Y	3.551
Yb	Yb–Yb	3.880
Zn (25°C)	Zn–Zn	2.6694
Zr	Zr–Zr	3.179